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Patentanmeldung Nr. Patent application No. Demande de brevet n°

03022235.0

**PRIORITY
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For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Bayer Aktiengesellschaft

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ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Tetrahydro-naphthalene derivatives

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TETRAHYDRO-NAPHTHALENE DERIVATIVESEPO - Munich
21

01. Okt. 2003

DETAILED DESCRIPTION OF INVENTION

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TECHNICAL FIELD

The present invention relates to a hydroxy-tetrahydro-naphthalene derivative which is useful as an active ingredient of pharmaceutical preparations. The hydroxy-tetrahydro-naphthalene derivative of the present invention has vanilloid receptor (VR1) antagonistic activity, and can be used for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of overactive bladder, urinary incontinence such as urge urinary incontinence, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, and inflammatory disorders such as asthma and chronic obstructive pulmonary (or airways) disease (COPD).

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BACKGROUND ART

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Vanilloid compounds are characterized by the presence of vanillyl group or a functionally equivalent group. Examples of several vanilloid compounds or vanilloid receptor modulators are vanillin (4-hydroxy-3-methoxy-benzaldehyde), guaiacol (2-methoxy-phenol), zingerone (4-(4-hydroxy-3-methoxyphenyl)-2-butanone), eugenol- (2-methoxy-4-(2-propenyl)-phenol), and capsaicin (8-methy-N-vanillyl-6-nonene- amide).

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Among others, capsaicin, the main pungent ingredient in "hot" chili peppers, is a specific neurotoxin that desensitizes C-fiber afferent neurons. Capsaicin interacts with vanilloid receptors (VR1), which are predominantly expressed in cell bodies of dorsal root ganglia (DRG) or nerve endings of afferent sensory fibers including C-

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fiber nerve endings [Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D: The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron. 21: 531-543, 1998]. The VR1 receptor was recently cloned [Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D: Nature 389: 816-824, (1997)] and identified as a non-selective cation channel with six transmembrane domains that is structurally related to the TRP (transient receptor potential) channel family. Binding of capsaicin to VR1 allows sodium, calcium and possibly potassium ions to flow down their concentration gradients, causing initial depolarization and release of neurotransmitters from the nerve terminals. VR1 can therefore be viewed as a molecular integrator of chemical and physical stimuli that elicit neuronal signals in pathological conditions or diseases.

There is abundant direct or indirect evidence that shows the relation between VR1 activity and diseases such as pain, ischaemia, and inflammatory disorders (e.g., WO 99/00115 and 00/50387). Further, it has been demonstrated that VR1 transduces reflex signals that are involved in the overactive bladder of patients who have damaged or abnormal spinal reflex pathways [De Groat WC: A neurologic basis for the overactive bladder. Urology 50 (6A Suppl): 36-52, 1997]. Desensitisation of the afferent nerves by depleting neurotransmitters using VR1 agonists such as capsaicin has been shown to give promising results in the treatment of bladder dysfunction associated with spinal cord injury and multiple sclerosis [(Maggi CA: Therapeutic potential of capsaicin-like molecules - Studies in animals and humans. Life Sciences 51: 1777-1781, 1992) and (DeRidder D; Chandiramani V; Dasgupta P; VanPoppel H; Baert L; Fowler CJ: Intravesical capsaicin as a treatment for refractory detrusor hyperreflexia: A dual center study with long-term followup. J. Urol. 158: 2087-2092, 1997)].

It is anticipated that antagonism of the VR1 receptor would lead to the blockage of neurotransmitter release, resulting in prophylaxis and treatment of the conditions and diseases associated with VR1 activity.

It is therefore expected that antagonists of the VR1 receptor can be used for prophylaxis and treatment of the conditions and diseases including chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algnesia, nerve injury, ischaemia, neurodegeneration, stroke, inflammatory disorders, urinary incontinence (UI) such as urge urinary incontinence (UUI), and/or overactive bladder.

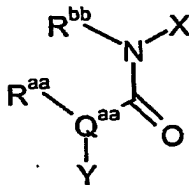
UI is the involuntary loss of urine. UUI is one of the most common types of UI together with stress urinary incontinence (SUI) which is usually caused by a defect in the urethral closure mechanism. UUI is often associated with neurological disorders or diseases causing neuronal damages such as dementia, Parkinson's disease, multiple sclerosis, stroke and diabetes, although it also occurs in individuals with no such disorders. One of the usual causes of UUI is overactive bladder (OAB) which is a medical condition referring to the symptoms of frequency and urgency derived from abnormal contractions and instability of the detrusor muscle.

There are several medications for urinary incontinence on the market today mainly to help treating UUI. Therapy for OAB is focused on drugs that affect peripheral neural control mechanisms or those that act directly on bladder detrusor smooth muscle contraction, with a major emphasis on development of anticholinergic agents. These agents can inhibit the parasympathetic nerves which control bladder voiding or can exert a direct spasmolytic effect on the detrusor muscle of the bladder. This results in a decrease in intravesicular pressure, an increase in capacity and a reduction in the frequency of bladder contraction. Orally active anticholinergic drugs such as propantheline (ProBanthine), tolterodine tartrate (Detrol) and oxybutynin (Ditropan) are the most commonly prescribed drugs. However, their most serious drawbacks are unacceptable side effects such as dry mouth, abnormal visions, constipation, and central nervous system disturbances. These side effects lead to poor compliance. Dry mouth symptoms alone are responsible for a 70% non-compliance rate with oxy-

butynin. The inadequacies of present therapies highlight the need for novel, efficacious, safe, orally available drugs that have fewer side effects.

WO03/014064 discloses the compounds represented by the general formula:

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wherein

10 X represents C₃₋₈ cycloalkyl optionally fused by benzene, optionally substituted naphthyl, optionally substituted phenyl, optionally substituted phenyl C₁₋₆ straight alkyl, phenyl fused by cycloalkyl, etc;

Q^{aa} represents CH or N;

15 R^{aa} represents hydrogen or methyl;

R^{bb} represents hydrogen or methyl; and

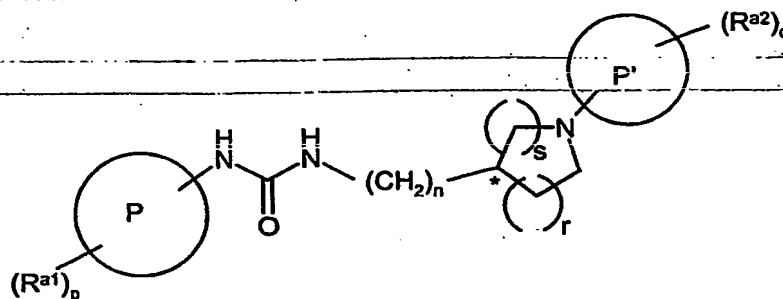
Y represents substituted naphthyl,

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as a vanilloid receptor antagonist.

WO03/022809 discloses the compounds having vanilloid receptor antagonist activity represented by the general formula:

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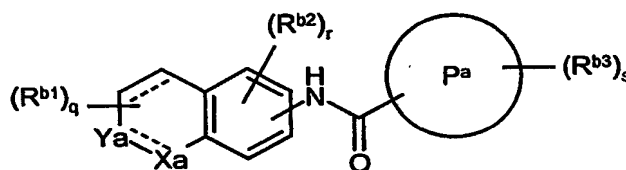
wherein

P and P' independently represent aryl or heteroaryl;

R^{a1} and R^{a2} independently represent hydrogen, alkoxy, hydroxy, etc;

n is 0, 1, 2 or 3; p and q are independently 0, 1, 2, 3 or 4; r is 1, 2 or 3; and s is 0, 1 or 2.

WO03/068749 discloses the compounds having vanilloid receptor antagonist activity represented by the general formula:



wherein

P^a represents phenyl, heteroaryl or heterocyclyl;

R^{b1} and R^{b2} independently represent halogen, alkoxy, hydroxy, etc;

R^{b3} represents alkyl, CF₃, alkoxy, optionally substituted phenyl, optionally substituted pyridyl etc;

q and r are independently 0, 1, 2 or 3; s is 0, 1, 2, or 3; and

Xa and Ya are selected from the following combinations;

- 5 Xa is N and Ya is CR^{b9} ; Xa is NR^{b8} and Ya is $C(R^{b9})_2$; Xa is CR^{b9} and Ya is N; Xa is $C(R^{b9})_2$ and Ya is NR^{b8} , wherein R^{b8} and R^{b9} are defined in the application.

However, none of these reference discloses hydroxy-tetrahydro-naphthalene derivatives having VR1 antagonistic activity.

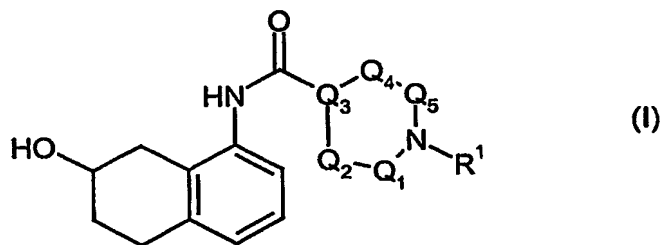
- 10 The development of a compound which has effective VR1 antagonistic activity and can be used for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urinary incontinence, urge urinary incontinence, overactive bladder as well as pain, and/or inflammatory diseases such as asthma and COPD has been desired.

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SUMMARY OF THE INVENTION

This invention is to provide a hydroxy-tetrahydro-naphthalene derivatives of the formula (I), their tautomeric and stereoisomeric form, and salts thereof:

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wherein

Q₁, Q₂, Q₄ and Q₅ independently represent $C(R^{11})(R^{12})$,

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wherein

R^{11} and R^{12} independently represent hydrogen, phenyl, benzyl, or C_{1-6} alkyl optionally substituted by hydroxy, carboxy, phenyl, benzyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino;

5 Q_3 represents $C-R^{13}$,

wherein

10 R^{13} represents hydrogen, phenyl, benzyl, or C_{1-6} alkyl optionally substituted by hydroxy, carboxy, phenyl, benzyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino;

R^1 represents C_{1-6} alkyl substituted by aryl or heteroaryl,

15 wherein

said aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, hydroxy, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-8} cycloalkylamino, C_{1-6} alkoxycarbonyl, phenyl, benzyl, heterocycle, sulfonamide, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, carbamoyl, C_{1-6} alkylcarbamoyl, cyano, C_{1-6} alkyl optionally substituted by cyano, C_{1-6} alkoxycarbonyl or mono-, di-, or tri-halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri-halogen, phenoxy optionally substituted by halogen or C_{1-6} alkyl, or C_{1-6} alkylthio optionally substituted by mono-, di-, or tri-halogen, C_{3-8} cycloalkyl, and heterocycle;

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or

aryl or heteroaryl,

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wherein

said aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, hydroxy, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₃₋₈ cycloalkylamino, C₁₋₆ alkoxycarbonyl, phenyl, benzyl, heterocycle, sulfonamide, C₁₋₆ alkanoyl, C₁₋₆ alkanoylamino, carbamoyl, C₁₋₆ alkylcarbamoyl, cyano, C₁₋₆ alkyl optionally substituted by cyano, C₁₋₆ alkoxycarbonyl or mono-, di-, or tri-halogen, C₁₋₆ alkoxy optionally substituted by mono-, di-, or tri- halogen, phenoxy optionally substituted by halogen or C₁₋₆ alkyl, or C₁₋₆ alkylthio optionally substituted by mono-, di-, or tri-halogen, C₃₋₈ cycloalkyl, and heterocycle.

In another embodiment, the hydroxy-tetrahydro-naphthalenylurea derivatives of formula (I) can be those wherein;

R¹ represents C₁₋₂ alkyl substituted by phenyl, naphthyl, pyridyl, or pyrimidyl,

wherein

said phenyl, naphthyl, pyridyl and pyrimidyl are optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₃₋₈ cycloalkylamino, C₁₋₆ alkoxycarbonyl, phenyl, benzyl, C₁₋₆ alkanoyl, C₁₋₆ alkanoylamino, carbamoyl, C₁₋₆ alkylcarbamoyl, cyano, C₁₋₆ alkyl optionally substituted by mono-, di-, or tri-halogen, C₁₋₆ alkoxy optionally substituted by mono-, di-, or tri- halogen, phenoxy optionally substituted by halogen or C₁₋₆ alkyl, or C₁₋₆ alkylthio optionally substituted by mono-, di-, or tri- halogen;

or

phenyl, naphthyl, pyridyl, or pyrimidyl

wherein

5 said phenyl, naphthyl, pyridyl and pyrimidyl are optionally substituted with
one or more substituents selected from the group consisting of halogen, nitro,
C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₃₋₈ cycloalkylamino, C₁₋₆ alkoxy-
carbonyl, phenyl, benzyl, C₁₋₆ alkanoyl, C₁₋₆ alkanoylamino, carbamoyl, C₁₋₆
alkylcarbamoyl, cyano, C₁₋₆ alkyl optionally substituted by mono-, di-, or tri-
halogen, C₁₋₆ alkoxy optionally substituted by mono-, di-, or tri- halogen,
10 phenoxy optionally substituted by halogen or C₁₋₆ alkyl, or C₁₋₆ alkylthio
optionally substituted by mono-, di-, or tri- halogen.

In another embodiment, the hydroxy-tetrahydro-naphthalenylurea derivatives of
formula (I) can be those wherein;

15

R¹ represents phenyl, pyridyl, or pyrimidyl,

wherein

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said phenyl, pyridyl and pyrimidyl are optionally substituted with one or
more substituents selected from the group consisting of halogen, nitro, C₁₋₆
alkylamino, di(C₁₋₆ alkyl)amino, C₃₋₈ cycloalkylamino, C₁₋₆ alkoxy carbonyl,
phenyl, benzyl, C₁₋₆ alkanoyl, C₁₋₆ alkanoylamino, carbamoyl, C₁₋₆ alkyl-
carbamoyl, cyano, C₁₋₆ alkyl optionally substituted by mono-, di-, or tri-
25 halogen, C₁₋₆ alkoxy optionally substituted by mono-, di-, or tri- halogen,
phenoxy optionally substituted by halogen or C₁₋₆ alkyl, or C₁₋₆ alkylthio
optionally substituted by mono-, di-, or tri- halogen.

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Preferably, the hydroxy-tetrahydro-naphthalene derivative of formula (I) are those
wherein;

Q₁, Q₂, Q₄ and Q₅ represent CH₂;

Q₃ represents CH;

5 R¹ represents phenyl, pyridyl, or pyrimidyl

wherein

10 said phenyl, pyridyl and pyrimidyl are optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, nitro, methoxy, trifluoromethyl, trifluoromethoxy and C₁₋₆ alkanoylamino.

More preferably, said hydroxy-tetrahydro-naphthalene derivative of the formula (I) is selected from the group consisting of:

15

1-(2-Chlorophenyl)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)piperidine-4-carboxamide;

N-(7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-1-(2-nitrophenyl)piperidine-4-carboxamide;

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N-(7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-1-[2-nitro-4-(trifluoromethyl)phenyl]piperidine-4-carboxamide;

1-(2-Fluorophenyl)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)piperidine-4-carboxamide;

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1-(4-Fluorophenyl)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)piperidine-4-carboxamide;

1-[4-Chloro-2-(trifluoromethyl)phenyl]-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)piperidine-4-carboxamide;

N-(7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-1-[4-(trifluoromethyl)phenyl]piperidine-4-carboxamide;

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1-[2-Chloro-4-(trifluoromethyl)phenyl]-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)piperidine-4-carboxamide;

1-(4-Fluorophenyl)-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-
piperidine-4-carboxamide;

1-(4-Fluorophenyl)-N-[(7S)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-
4-carboxamide;

5 1-[2-Chloro-4-(trifluoromethyl)phenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydro-
naphthalen-1-yl]piperidine-4-carboxamide;

1-[2-Chloro-4-(trifluoromethyl)phenyl]-N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-
naphthalen-1-yl]piperidine-4-carboxamide;

10 1-[3-Chlorophenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-
piperidine-4-carboxamide;

N-[(7R)-7-Hydroxy-1-phenyl-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-
carboxamide;

N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[3-trifluoromethyl-
phenyl]piperidine-4-carboxamide;

15 N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[3-trifluoromethoxy-
phenyl]piperidine-4-carboxamide;

1-[2,4-Dichlorophenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-
yl]piperidine-4-carboxamide;

20 1-[3,4-Bis(trifluoromethoxy)phenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydro-
naphthalen-1-yl]piperidine-4-carboxamide;

N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[4-trifluoromethoxy-
phenyl]piperidine-4-carboxamide;

N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[4-trifluoromethyl-
pyrimidin-2-yl]-piperidine-4-carboxamide;

25 1-[5-Chloropyrimidin-2-yl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-
yl]piperidine-4-carboxamide;

1-[2-Chloro-4-nitrophenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-
yl]piperidine-4-carboxamide;

30 1-[3-(Acetylamino)-5-(trifluoromethyl)pyridin-2-yl]-N-[(7R)-7-hydroxy-5,6,7,8-
tetrahydronaphthalen-1-yl]piperidine-4-carboxamide;

N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[5-(trifluoromethyl)-pyridin-2-yl]piperidine-4-carboxamide; and

N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[4-trifluoromethyl-phenyl]piperidine-4-carboxamide.

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The tetrahydro-naphthalene derivatives of formula (I), their tautomeric and stereoisomeric form, and salts thereof surprisingly show excellent VR1 antagonistic activity. They are, therefore suitable especially for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urinary incontinence, urge urinary incontinence and/or overactive bladder.

10

The compounds of the present invention are also effective for treating or preventing a disease selected from the group consisting of chronic pain, neuropathic pain, post-operative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration and/or stroke, as well as inflammatory diseases such as asthma and COPD since the diseases also relate to VR1 activity.

15

The compounds of the present invention are also useful for the treatment and prophylaxis of neuropathic pain, which is a form of pain often associated with herpes zoster and post-herpetic neuralgia, painful diabetic neuropathy, neuropathic low back pain, posttraumatic and postoperative neuralgia, neuralgia due to nerve compression and other neuralgias, phantom pain, complex regional pain syndromes, infectious or parainfectious neuropathies like those associated with HIV infection, pain associated with central nervous system disorders like multiple sclerosis or Parkinson disease or spinal cord injury or traumatic brain injury, and post-stroke pain.

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Furthermore, the compounds of the present invention are useful for the treatment of musculoskeletal pain, forms of pain often associated with osteoarthritis or rheumatoid arthritis or other forms of arthritis, and back pain.

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In addition, the compounds of the present invention are useful for the treatment of pain associated with cancer, including visceral or neuropathic pain associated with cancer or cancer treatment.

5 The compounds of the present invention are furthermore useful for the treatment of visceral pain, e.g. pain associated with obstruction of hollow viscus like gallstone colik, pain associated with irritable bowel syndrome, pelvic pain, vulvodynia, orchialgia or prostatodynia, pain associated with inflammatory lesions of joints, skin, muscles or nerves, and orofascial pain and headache, e.g. migraine or tension-type
10 headache.

Further, the present invention provides a medicament, which includes one of the compounds, described above and optionally pharmaceutically acceptable excipients.

15 Alkyl per se and "alk" and "alkyl" in alkenyl, alkynyl, alkoxy, alkanoyl, alkylamino, alkylaminocarbonyl, alkylaminosulfonyl, alkylsulfonylamino, alkoxycarbonyl, alkoxycarbonylamino and alkanoylamino represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl,
20 tert-butyl, n-pentyl and n-hexyl.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

25 Alkylamino illustratively and preferably represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino,
30 N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

Cycloalkyl per se and in cycloalkylamino and in cycloalkylcarbonyl represents a cycloalkyl group having generally 3 to 8 and preferably 5 to 7 carbon atoms, illustratively and preferably representing cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

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Heterocyclyl per se and in heterocyclylcarbonyl represents a mono- or polycyclic, preferably mono- or bicyclic, nonaromatic heterocyclic radical having generally 4 to 10 and preferably 5 to 8 ring atoms and up to 3 and preferably up to 2 hetero atoms and/or hetero groups selected from the group consisting of N, O, S, SO and SO₂. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5- to 8-membered monocyclic saturated heterocyclyl radicals having up to two hetero atoms selected from the group consisting of O, N and S, such as illustratively and preferably tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholinyl, perhydroazepinyl.

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EMBODIMENT OF THE INVENTION

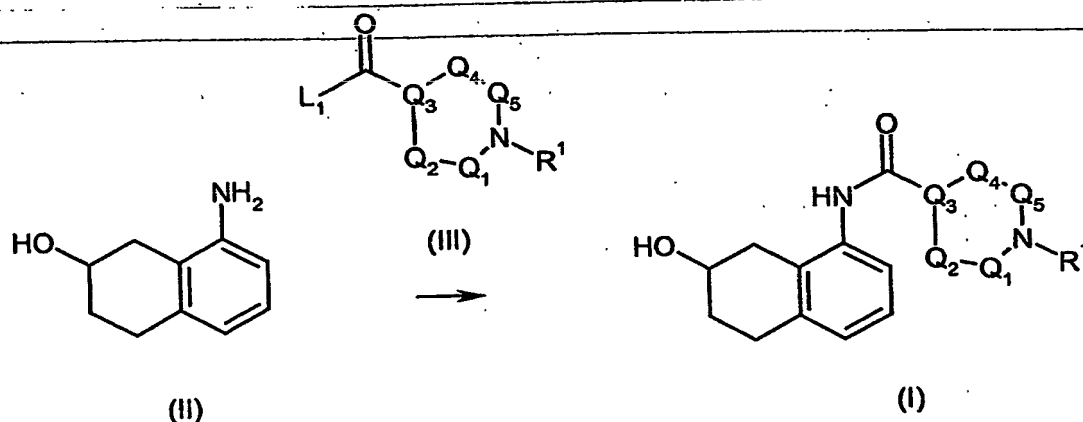
The compound of the formula (I) of the present invention can be, but not limited to be, prepared by combining various known methods. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (3rd Edition)" by Greene and Wuts, John Wiley and Sons, New York 1999.

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The compound of the formula (I) of the present invention can be, but not limited to be, prepared by the Method [A] below.

[Method A]



The compound of the formula (I) (wherein Q₁, Q₂, Q₃, Q₄, Q₅ and R¹ are the same as defined) can be prepared by the reaction of the compound of the formula (II) with the compound of the formula (III) (wherein Q₁, Q₂, Q₃, Q₄, Q₅ and R¹ are the same as defined above and L₁ represents a leaving group including, for instance, hydroxy, halogen atom such as chlorine, bromine, or iodine atom, or azole such as imidazole or triazole.).

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); ureas such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 0°C to 50°C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

The reaction can be advantageously carried out in the presence of a base including, for instance, organic amines such as pyridine, triethylamine and N,N-diisopropylethylamine, dimethylaniline, diethylaniline, 4-dimethylaminopyridine, and others.

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When L₁ is hydroxy, the reaction can be advantageously carried out using coupling agent including, for instance, hydroxybenzotriazole, carbodiimides such as N,N-dicyclohexylcarbodiimide and 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide; carbonyldiazoles such as 1,1'-carbonyldi(1,3-imiazole)(CDI) and 1,1'-carbonyldi(1,2,4-triazole)(CDT), and the like.

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The compound (II) and (III) are commercially available or can be prepared by the use of known techniques.

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When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

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Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

25

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

30

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal

hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salt thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring

agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients therefore. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carriers, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg /kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven

advantageous to administer quantities of about 0.001 to 100mg /kg/day, preferably
from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may
be administered in a single daily dose, or the total daily dose may be administered in
divided doses, two, three, or more times per day. Where delivery is via transdermal
5 forms, of course, administration is continuous.

EXAMPLES

The present invention will be described as a form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

5

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

The following abbreviations are used in the descriptions:

10

appx. = approximately

aq. = aqueous

DMSO = dimethyl sufoxide

eq. = equivalent

15 HPLC = High Pressure Liquid Chromatography

LCMS = Liquid Chromatography coupled with Mass Spectroscopy

min. = minute

MS = Mass Spectroscopy

RP-HPLC = Reverse Phase High Pressure Liquid Chromatography

20 R_t = retention time

TLC = Thin Layer Chromatography

HPLC- and LCMS-Methods:

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Method A (HPLC)

instrument: HP 1100 with DAD-detektion; column: Kromasil RP-18, 60 mm x 2 mm, 3.5 μ m; eluent A: 5 ml HClO₄/l water, eluent B: acetonitrile; gradient: 0 min 2%B, 0.5 min 2%B, 4.5 min 90%B, 6.5 min 90%B; flow rate: 0.75 ml/min; oven: 30°C; UV-detektion: 210 nm.

30

Method B (HPLC)

instrument: HP 1100 with DAD-detektion; column: Kromasil RP-18, 60 mm x 2 mm, 3.5 µm; eluent A: 5 ml HClO₄/l water, eluent B: acetonitrile; gradient: 0 min 2%B, 0.5 min 2%B, 4.5 min 90%B, 9 min 90%B; flow rate: 0.75 ml/min; oven: 30°C; UV-detektion: 210 nm.

Method C (preparative RP-HPLC)

Column: GROM-SIL 120 ODS-4 HE 10 µm, 250 mm x 30 mm; acetonitrile/water gradients

Method D (LCMS)

instrument: Micromass Quattro LCZ with HPLC Agilent Serie 1100; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm x 4 mm; eluent A: 1 l water + 0.5 ml 50% formic acid, eluent B: 1 l acetonitrile + 0.5 ml 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV-detektion: 208- 400 nm.

Liquid Chromatography - Mass spectroscopy (LC-MS)

Micromass Platform LC with Shimadzu Phenomenex ODS column(4.6 mmφ X 30 mm) flushing a mixture of acetonitrile-water (9:1 to 1:9) at 1 ml/min of the flow rate.

Mass spectra

Electrospray (ES) ionization techniques (ESI) : Perkin Elmer/SCIEX API 150MCA
Direct chemical ionization (DCI) : Finnigan MAT 95

Mass determinations

Finnigan MAT MAT95

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Melting points are uncorrected.

¹H NMR spectra were recorded using either Bruker DRX-300 (300 MHz for ¹H) spectrometer, Bruker 500 UltraShieldTM (500 MHz for ¹H), Bruker Avance 300 (300 MHz for ¹H) or Bruker Avance 400 (400 MHz for ¹H). Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. The abbreviations s, d, t, q, m, and br refer to singlet, doublet, triplet, quartet, multiplet, and broad, respectively.

All starting materials are commercially available or can be prepared using methods cited in the literature.

The effect of the present compounds was examined by the following assays and pharmacological tests.

[Measurement of capsaicin-induced Ca²⁺ influx in the human VR1-transfected CHO cell line] (Assay 1)

(1) Establishment of the human VR1-CHOluc9aeq cell line

Human vanilloid receptor (hVR1) cDNA was cloned from libraries of axotomized dorsal root ganglia (WO 00/29577). The cloned hVR1 cDNA was constructed with pcDNA3 vector and transfected into a CHOluc9aeq cell line. The cell line contains aequorin and CRE-luciferase reporter genes as read-out signals. The transfectants were cloned by limiting dilution in selection medium (DMEM/F12 medium (Gibco BRL) supplemented with 10% FCS, 1.4 mM Sodium pyruvate, 20 mM HEPES, 0.15% Sodium bicarbonate, 100 U/ml penicillin, 100 µg/ml streptomycin, 2 mM glutamine, non-essential amino acids and 2 mg/ml G418). Ca²⁺ influx was examined in the capsaicin-stimulated clones. A high responder clone was selected and used for further experiments in the project. The human VR1-CHOluc9aeq cells were

maintained in the selection medium and passaged every 3-4 days at $1-2.5 \times 10^5$ cells/flask (75 mm^2).

(2) Measurement of Ca^{2+} influx using FDSS-3000

5

Human VR1-CHOluc9aeq cells were suspended in a culture medium which is the same as the selection medium except for G418 and seeded at a density of 1,000 cells per well into 384-well plates (black walled clear-base / Nalge Nunc International). Following the culture for 48 hrs the medium was changed to $2 \mu\text{M}$ Fluo-3 AM (Molecular Probes) and 0.02% Puroic F-127 in assay buffer (Hank's balanced salt solution (HBSS), 17 mM HEPES (pH7.4), 1 mM Probenecid, 0.1% BSA) and the cells were incubated for 60 min at 25°C . After washing twice with assay buffer the cells were incubated with a test compound or vehicle for 20 min at 25°C . Mobilization of cytoplasmic Ca^{2+} was measured by FDSS-3000 ($\lambda_{\text{ex}}=488\text{nm}$, $\lambda_{\text{em}}=540\text{nm}$ / Hamamatsu Photonics) for 60 sec after the stimulation with 10 nM capsaicin. Integral R was calculated and compared with controls.

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[Measurement of the capsaicin-induced Ca^{2+} influx in primary cultured rat dorsal root ganglia neurons] (Assay 2)

(1) Preparation of rat dorsal root ganglia neurons

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New born Wister rats (5-11 days) were sacrificed and dorsal root ganglia (DRG) was removed. DRG was incubated with 0.1% trypsin (Gibco BRL) in PBS(-) (Gibco BRL) for 30 min at 37°C , then a half volume of fetal calf serum (FCS) was added and the cells were spun down. The DRG neuron cells were resuspended in Ham F12/5% FCS/5% horse serum (Gibco BRL) and dispersed by repeated pipetting and passing through $70 \mu\text{m}$ mesh (Falcon). The culture plate was incubated for 3 hours at 37°C to remove contaminating Schwann cells. Non-adherent cells were recovered and further cultured in

laminin-coated 384 well plates (Nunc) at 1×10^4 cells/50 μ l/well for 2 days in the presence of 50 ng/ml recombinant rat NGF (Sigma) and 50 μ M 5-fluorodeoxyuridine (Sigma).

5 (2) Ca^{2+} mobilization assay

10 DRG neuron cells were washed twice with HBSS supplemented with 17 mM HEPES (pH 7.4) and 0.1% BSA. After incubating with 2 μ M fluo-3AM (Molecular Probe), 0.02% PF127 (Gibco BRL) and 1 mM probenecid (Sigma) for 40 min at 37°C, cells were washed 3 times. The cells were incubated with VR1 antagonists or vehicle (dimethylsulfoxide) and then with 1 μ M capsaicin in FDSS-6000 (λ_{ex} =480nm, λ_{em} =520nm / Hamamatsu Photonics). The fluorescence changes at 480nm were monitored for 2.5 min. Integral R was calculated and compared with controls.

15

[Organ bath assay to measure the capsaicin-induced bladder contraction] (Assay 3)

20 Male Wistar rats (10 week old) were anesthetized with ether and sacrificed by dislocating the necks. The whole urinary bladder was excised and placed in oxygenated Modified Krebs-Henseleit solution (pH 7.4) of the following composition (112 mM NaCl, 5.9 mM KCl, 1.2 mM MgCl_2 , 1.2 mM NaH_2PO_4 , 2 mM CaCl_2 , 2.5 mM NaHCO_3 , 12 mM glucose). Contractile responses of the urinary bladder were studied as described previously [Maggi CA et al: Br.J.Pharmacol. 108: 801-805, 1993]. Isometric tension was recorded under a load of 1 g using longitudinal strips of rat detrusor muscle. Bladder strips were equilibrated for 60 min before each stimulation. Contractile response to 80 mM KCl was determined at 15 min intervals until reproducible responses were obtained. The response to KCl was used as an internal standard to evaluate the maximal response to capsaicin. The effects of the compounds were investigated by incubating the strips with compounds for 30 min prior to the stimulation with 1 μ M capsaicin (vehicle: 80% saline, 10% EtOH, and 10%

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Tween 80). One of the preparations made from the same animal was served as a control while the others were used for evaluating compounds. Ratio of each capsaicin-induced contraction to the internal standard (i.e. KCl-induced contraction) was calculated and the effects of the test compounds on the capsaicin-induced contraction were evaluated.

[Measurement of Ca^{2+} influx in the human P2X1-transfected CHO cell line]

(1) Preparation of the human P2X1-transfected CHO_{luc9aeq} cell line

Human P2X1-transfected CHO_{luc9aeq} cell line was established and maintained in Dulbecco's modified Eagle's medium (DMEM/F12) supplemented with 7.5% FCS, 20 mM HEPES-KOH (pH 7.4), 1.4 mM sodium pyruvate, 100 U/ml penicillin, 100 µg/ml streptomycin, 2 mM glutamine (Gibco BRL) and 0.5 Units/ml apyrase (grade I, Sigma). The suspended cells were seeded in each well of 384-well optical bottom black plates (Nalge Nunc International) at 3×10^3 / 50 µl / well. The cells were cultured for following 48 hrs to adhere to the plates.

(2) Measurement of the intracellular Ca^{2+} levels

P2X1 receptor agonist-mediated increases in cytosolic Ca^{2+} levels were measured using a fluorescent Ca^{2+} chelating dye, Fluo-3 AM (Molecular Probes). The plate-attached cells were washed twice with washing buffer (HBSS, 17 mM HEPES-KOH (pH 7.4), 0.1% BSA and 0.5 units/ml apyrase), and incubated in 40 µl of loading buffer (1 µM Fluo-3 AM, 1 mM probenecid, 1 µM cyclosporin A, 0.01% pluronic (Molecular Probes) in washing buffer) for 1 hour in a dark place. The plates were washed twice with 40 µl washing buffer and 35 µl of washing buffer were added in each well with 5 µl of test compounds or 2',3'-o-(2,4,6-trinitrophenyl) adenosine 5'-triphosphate (Molecular Probes) as a reference. After further incubation for

10 minutes in dark 200 nM α , β -methylene ATP agonist was added to initiate the Ca^{2+} mobilization. Fluorescence intensity was measured by FDSS-6000 ($\lambda_{\text{ex}}=410\text{nm}$, $\lambda_{\text{em}}=510\text{nm}$ / Hamamatsu Photonics) at 250 msec intervals. Integral ratios were calculated from the data and compared with that of a control.

[Measurement of capsaicin-induced bladder contraction in anesthetized rats]
(Assay 4)

(1) Animals

Female Sprague-Dawley rats (200~250 g / Charles River Japan) were used.

(2) Catheter implantation

Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.2 g/kg. The abdomen was opened through a midline incision, and a polyethylene catheter (BECTON DICKINSON, PE50) was implanted into the bladder through the dome. In parallel, the inguinal region was incised, and a polyethylene catheter (Hibiki, size 5) filled with 2 IU / ml of heparin (Novo Heparin, Aventis Pharma) in saline (Otsuka) was inserted into a common iliac artery.

(3) Cystometric investigation

The bladder catheter was connected via T-tube to a pressure transducer (Viggo-Spectramed Pte Ltd, DT-XXAD) and a microinjection pump (TERUMO). Saline was infused at room temperature into the bladder at a rate of 2.4 ml/hr. Intravesical pressure was recorded continuously on a chart pen recorder (Yokogawa). At least three reproducible micturition cycles, corre-

sponding to a 20-minute period, were recorded before a test compound administration and used as baseline values.

(4) Administration of test compounds and stimulation of bladder with capsaicin

5

The saline infusion was stopped before administering compounds. A testing compound dissolved in the mixture of ethanol, Tween 80 (ICN Biomedicals Inc.) and saline (1 : 1 : 8, v/v/v) was administered intraarterially at 10 mg/kg. 2min after the administration of the compound 10 µg of capsaicin (Nacalai Tesque) dissolved in ethanol was administered intraarterially.

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(5) Analysis of cystometry parameters

Relative increases in the capsaicin-induced intravesical pressure were analyzed from the cystometry data. The capsaicin-induced bladder pressures were compared with the maximum bladder pressure during micturition without the capsaicin stimulation. The testing compounds-mediated inhibition of the increased bladder pressures was evaluated using Student's t-test. A probability level less than 5% was accepted as significant difference.

20

[Measurement of over active bladder in anesthetized cystitis rats] (Assay 5)

(1) Animals

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Female Sprague-Dawley rats (180~250 g / Charles River Japan) were used. Cyclophosphamide (CYP) dissolved in saline was administered intraperitoneally at 150 mg/kg 48 hours before experiment.

(2) Catheter implantation

5 Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.25 g/kg. The abdomen was opened through a midline incision, and a polyethylene catheter (BECTON DICKINSON, PE50) was implanted into the bladder through the dome. In parallel, the inguinal region was incised, and a polyethylene catheter (BECTON DICKINSON, PE50) filled with saline (Otsuka) was inserted into a femoral vein. After the bladder was emptied, the rats were left for 1 hour for recovery from the operation.

10

(3) Cystometric investigation

15 The bladder catheter was connected via T-tube to a pressure transducer (Viggo-Spectramed Pte Ltd, DT-XXAD) and a microinjection pump (TERUMO). Saline was infused at room temperature into the bladder at a rate of 3.6 ml/hr for 20 min. Intravesical pressure was recorded continuously on a chart pen recorder (Yokogawa). At least three reproducible micturition cycles, corresponding to a 20-minute period, were recorded before a test compound administration.

20

(4) Administration of test compounds

25 A testing compound dissolved in the mixture of ethanol, Tween 80 (ICN Biomedicals Inc.) and saline (1 : 1 : 8, v/v/v) was administered intravenously at 0.05 mg/kg, 0.5 mg/kg or 5 mg/kg. 3min after the administration of the compound, saline (Nacalai Tesque) was infused at room temperature into the bladder at a rate of 3.6 ml/hr.

(5) Analysis of cystometry parameters

5 The cystometry parameters were analyzed as described previously [Lecci A
et al: Eur. J. Pharmacol. 259: 129-135, 1994]. The micturition frequency
calculated from micturition interval and the bladder capacity calculated from
a volume of infused saline until the first micturition were analyzed from the
cystometry data. The testing compounds-mediated inhibition of the frequency
and the testing compounds-mediated increase of bladder capacity were
evaluated using unpaired Student's t-test. A probability levels less than 5%
10 was accepted as significant difference. Data were analyzed as the mean \pm
SEM from 4 – 7 rats.

[Measurement of Acute Pain]

15 Acute pain is measured on a hot plate mainly in rats. Two variants of hot plate testing
are used: In the classical variant animals are put on a hot surface (52 to 56°C) and the
latency time is measured until the animals show nociceptive behavior, such as
stepping or foot licking. The other variant is an increasing temperature hot plate
where the experimental animals are put on a surface of neutral temperature.
20 Subsequently this surface is slowly but constantly heated until the animals begin to
lick a hind paw. The temperature which is reached when hind paw licking begins is a
measure for pain threshold.

Compounds are tested against a vehicle treated control group. Substance application
25 is performed at different time points via different application routes (i.v., i.p., p.o.,
i.t., i.c.v., s.c., intradermal, transdermal) prior to pain testing.

[Measurement of Persistent Pain]

30 Persistent pain is measured with the formalin or capsaicin test, mainly in rats. A
solution of 1 to 5% formalin or 10 to 100 μ g capsaicin is injected into one hind paw

of the experimental animal. After formalin or capsaicin application the animals show nociceptive reactions like flinching, licking and biting of the affected paw. The number of nociceptive reactions within a time frame of up to 90 minutes is a measure for intensity of pain.

5

Compounds are tested against a vehicle treated control group. Substance application is performed at different time points via different application routes (i.v., i.p., p.o., i.t., i.c.v., s.c., intradermal, transdermal) prior to formalin or capsaicin administration.

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[Measurement of Neuropathic Pain]

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Neuropathic pain is induced by different variants of unilateral sciatic nerve injury mainly in rats. The operation is performed under anesthesia. The first variant of sciatic nerve injury is produced by placing loosely constrictive ligatures around the common sciatic nerve (Bennett and Xie, Pain 33 (1988): 87-107). The second variant is the tight ligation of about the half of the diameter of the common sciatic nerve (Seltzer et al., Pain 43 (1990): 205-218). In the next variant, a group of models is used in which tight ligations or transections are made of either the L5 and L6 spinal nerves, or the L5 spinal nerve only (KIM SH; CHUNG JM, AN EXPERIMENTAL-MODEL FOR PERIPHERAL NEUROPATHY PRODUCED BY SEGMENTAL SPINAL NERVE LIGATION IN THE RA, PAIN 50 (3) (1992): 355-363). The fourth variant involves an axotomy of two of the three terminal branches of the sciatic nerve (tibial and common peroneal nerves) leaving the remaining sural nerve intact whereas the last variant comprises the axotomy of only the tibial branch leaving the sural and common nerves uninjured. Control animals are treated with a sham operation.

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Postoperatively, the nerve injured animals develop a chronic mechanical allodynia, cold allodynia, as well as a thermal hyperalgesia. Mechanical allodynia is measured by means of a pressure transducer (electronic von Frey Anesthesiometer, IITC Inc.-Life Science Instruments, Woodland Hills, SA, USA; Electronic von Frey System,

Somedic Sales AB, Hörby, Sweden). Thermal hyperalgesia is measured by means of a radiant heat source (Plantar Test, Ugo Basile, Comerio, Italy), or by means of a cold plate of 5 to 10 °C where the nocifensive reactions of the affected hind paw are counted as a measure of pain intensity. A further test for cold induced pain is the counting of nocifensive reactions, or duration of nocifensive responses after plantar administration of acetone to the affected hind limb. Chronic pain in general is assessed by registering the circadian rhythms in activity (Surjo and Arndt, Universität zu Köln, Cologne, Germany), and by scoring differences in gait (foot print patterns; FOOTPRINTS program, Klapdor et al., 1997. A low cost method to analyse footprint patterns. J. Neurosci. Methods 75, 49-54).

Compounds are tested against sham operated and vehicle treated control groups. Substance application is performed at different time points via different application routes (i.v., i.p., p.o., i.t., i.c.v., s.c., intradermal, transdermal) prior to pain testing.

[Measurement of Inflammatory Pain]

Inflammatory pain is induced mainly in rats by injection of 0.75 mg carrageenan or complete Freund's adjuvant into one hind paw. The animals develop an edema with mechanical allodynia as well as thermal hyperalgesia. Mechanical allodynia is measured by means of a pressure transducer (electronic von Frey Anesthesiometer, IITC Inc.-Life Science Instruments, Woodland Hills, SA, USA). Thermal hyperalgesia is measured by means of a radiant heat source (Plantar Test, Ugo Basile, Comerio, Italy, Paw thermal stimulator, G. Ozaki, University of California, USA). For edema measurement two methods are being used. In the first method, the animals are sacrificed and the affected hindpaws sectioned and weighed. The second method comprises differences in paw volume by measuring water displacement in a plethysmometer (Ugo Basile, Comerio, Italy).

Compounds are tested against uninflamed as well as vehicle treated control groups.

Substance application is performed at different time points via different application

routes (i.v., i.p., p.o., i.t., i.c.v., s.c., intradermal, transdermal) prior to pain testing.

5 [Measurement of Diabetic Neuropathic Pain]

Rats treated with a single intraperitoneal injection of 50 to 80 mg/kg streptozotocin develop a profound hyperglycemia and mechanical allodynia within 1 to 3 weeks.

10 Mechanical allodynia is measured by means of a pressure transducer (electronic von Frey Anesthesiometer, IITC Inc.-Life Science Instruments, Woodland Hills, SA, USA).

Compounds are tested against diabetic and non-diabetic vehicle treated-control groups. Substance application is performed at different time points via different
15 application routes (i.v., i.p., p.o., i.t., i.c.v., s.c., intradermal, transdermal) prior to pain testing.

Results in capsaicin-induced Ca^{2+} influx assay in the human VR1-transfected CHO cell line (Assay 1) are shown in Examples and tables of the Examples below. For
20 practical reasons, the compounds are grouped in four classes based on activity as follows:

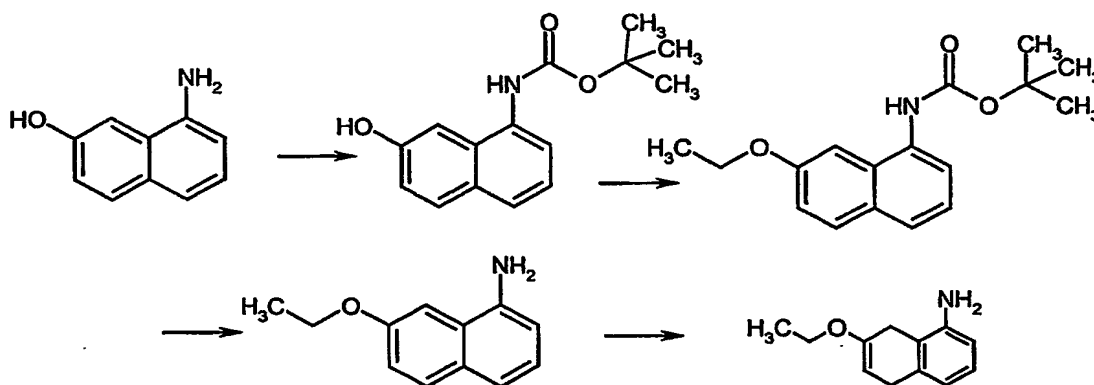
$$\text{IC}_{50} = \text{A} (< \text{ or } =) 0.1 \mu\text{M} < \text{B} (< \text{ or } =) 0.5 \mu\text{M} < \text{C} (< \text{ or } =) 1 \mu\text{M} < \text{D}$$

25 The compounds of the present invention also show excellent selectivity, and strong activity in other assays 2-5 and assays for pain described above.

Preparing method of starting compounds

[Starting compound 1S]

5 (7-Ethoxy-5,8-dihydronaphthalen-1-yl)amine



To a stirred solution of 8-amino-2-naphthol (50.0 g, 314 mmol) in tetrahydrofuran (1000 ml) was added di-*t*-butyldicarbonate (68.6 g, 314 mmol). The mixture was stirred at 70°C for 18 hours. After the mixture was cooled to room temperature, solvent was removed under reduced pressure. To the residue was added ethylacetate, and washed with saturated aqueous solution of sodium carbonate and then with water. The extracted organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. To the obtained residue was added diisopropyl ether, and the precipitate was filtered and dried to afford *tert*-butyl (7-hydroxy-1-naphthyl)-carbamate (64.2 g, 79 % yield).

Next, to a mixture of *tert*-butyl (7-hydroxy-1-naphthyl)carbamate (64.0 g, 247 mmol) and Cesium carbonate (161 g, 493 mmol) in 300 ml of anhydrous DMF was added iodoethane (42.3 g, 272 mmol) at room temperature. The mixture was stirred at 60°C for 2 hours. Water was added to the mixture, and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. To the obtained residue

was added diisopropyl ether and the precipitate was collected and dried to afford tert-butyl (7-ethoxy-1-naphthyl)carbamate (47.9 g, 67.5 % yield).

5 Next, to a solution of tert-butyl (7-ethoxy-1-naphthyl)carbamate (47.9 g, 167 mmol) in 100 ml of anhydrous 1,4-dioxane was added 4N HCl in 1,4-dioxane (100 ml) at 0°C. The mixture was stirred at room temperature for 2 hours. Diisopropyl ether was added to the reaction mixture and the precipitate was filtered. To the obtained solid was added saturated sodium bicarbonate and the product was extracted with ethylacetate. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford (7-ethoxy-1-naphthyl)amine (27.0 g, 86.3 % yield).

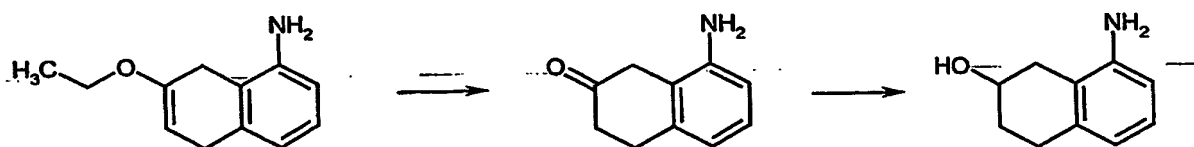
15 Next, to a mixture of (7-ethoxy-1-naphthyl)amine (1.80 g, 9.61 mmol) and t-buthanol (2.13 g, 28.8 mmol) in tetrahydrofuran (20 mL) was collected liquid ammonia (300 mL) at -78°C. To the mixture was added lithium (0.200 g, 28.8 mmol) over 30 minutes and stirred at -78°C for 1 hour. Methanol and water was added, and the mixture was stirred at room temperature for 16 hours to allow ammonia to evaporate. To the obtained residue was added ethyl acetate. The organic layer was washed with water, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford (7-ethoxy-5,8-dihydronaphthalen-1-yl)amine (1.37 g, 76 % yield).

20

[Starting compound 2S]

8-amino-1,2,3,4-tetrahydro-naphthalen-2-ol

25



To a stirred solution of (7-ethoxy-5,8-dihydronaphthalen-1-yl)amine (1.07 g, 5.65 mmol) in tetrahydrofuran (30 ml) was added solution of aqueous 2N HCl (10 mL), and stirred at 40°C for 1 hour. The mixture was neutralized with addition

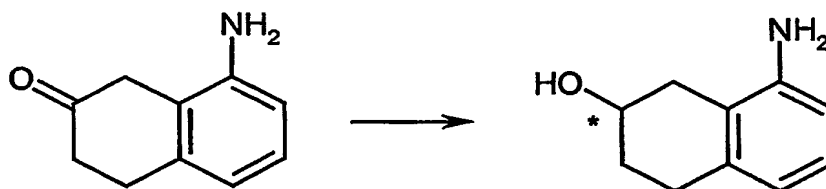
of sodium bicarbonate, and the product was extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to afford 8-amino-3,4-dihydronaphthalen-2(1H)-one (0.71 g, 78 % yield).

5

Next, to a solution of 8-amino-3,4-dihydronaphthalen-2(1H)-one (0.050 g, 0.318 mmol) in methanol (10 ml) was added sodium borohydride (0.030 g, 0.175 mmol) at 0°C , and the mixture was stirred for 1 hour. The mixture was poured into water, and the product was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to afford 8-amino-1,2,3,4-tetrahydro-naphthalen-2-ol (0.037 g, 71 % yield).

10

[Starting compound 3S]

15 **8-Amino-1,2,3,4-tetrahydro-naphthalen-2-ol (enantiomer)**

20

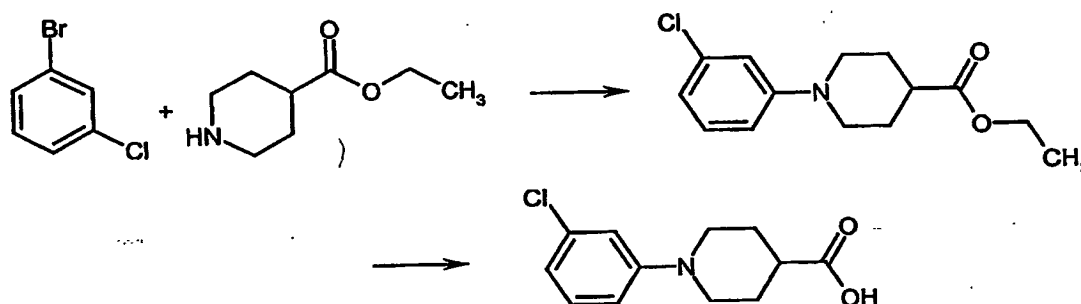
To a stirred solution of benzeneruthenium(II) chloride dimer (3.10 mg, 0.006 mmol) and (1S, 2R)-(-)-cis-1-amino-2-indanol (3.7 mg, 0.025 mmol) in degassed isopropanol was heated at 80°C for 20 minutes under argon. The mixture was added to the solution of 8-amino-3,4-dihydronaphthalen-2(1H)-one (50 mg, 0.310 mmol) in isopropanol (3 ml) at room temperature. A solution of potassium hydroxide (3.48 mg, 0.062 mmol) in isopropanol (1 mL) was added, and the mixture was stirred at 45°C for 1 hour. The mixture was passed through silica gel and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to afford 8-amino-1,2,3,4-tetrahydro-naphthalen-2-ol (enantiomer) (33.0 mg, 65% yield).

25

The other enantiomer of 8-amino-1,2,3,4-tetrahydronaphthalen-2-ol was obtained in the same fashion replacing (1S,2R)-(-)-cis-1-amino-2-indanol with (1R,2S)-(+)-cis-1-amino-2-indanol.

5 [Starting compound 4S]

(3-Chlorophenyl)-piperidine-4-carboxylic acid



10

In a dried, screwcapped test tube under argon to a mixture of 240 mg (2.49 mmol) sodium tert.-butanolate, 33 mg (0.04 mmol) of tris-(dibenzylideneacetone)-dipalladium(0) and 42 mg (0.11 mmol) of 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl in 3.1 ml of toluene were added 308 mg (1.96 mmol) of ethyl piperidine-4-carboxylate and 341 mg (1.78 mmol) of 3-chlorobromobenzene. The mixture was stirred with heating overnight at 80°C. After cooling, ethyl acetate was added, solid material was filtered off, the solvents were evaporated and the residue was purified by preparative RP-HPLC in a water/acetonitrile gradient to yield ethyl 1-(3-chlorophenyl)-piperidine-4-carboxylate.

15

20

^1H NMR (CDCl_3) δ 1.27 (t, 3H), 1.85 (dtd, 2H), 1.97-2.06 (m, 2H), 2.44 (tt, 1H), 2.81 (td, 2H), 3.63 (dt, 2H), 4.16 (q, 2H), 6.76-6.82 (m, 2H), 6.88 (t, 1H), 7.15 (t, 1H).

MS (DCI/ NH_3): $m/z = 268$ ($\text{M}+\text{H}$) $^+$

25

HPLC (method A): $R_t = 4.14$ min

158 mg (0.59 mmol) of ethyl 1-(3-chlorophenyl)-piperidine-4-carboxylate were dissolved in 2.30 ml of methanol and 0.3 ml of water, and 99 mg (1.77 mmol) of powdered potassium hydroxide were added. The mixture was stirred at room temperature overnight. After evaporation of the solvent, water was added and the mixture was acidified to pH 2-3 with 2N hydrochloric acid. The aqueous phase was extracted with ethyl acetate three times, the combined organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to give 127 mg (90% yield) of 1-(3-chlorophenyl)-piperidine-4-carboxylic acid.

¹H NMR (CDCl₃) δ 1.86 (dtd, 2H), 2.05-2.10 (m, 2H), 2.52 (tt, 1H), 2.84 (ddd, 2H), 3.64 (dt, 2H), 6.77-6.83 (m, 2H), 6.89 (t, 1H), 7.15 (t, 1H), 10.0-12.0 (very broad, 1H).

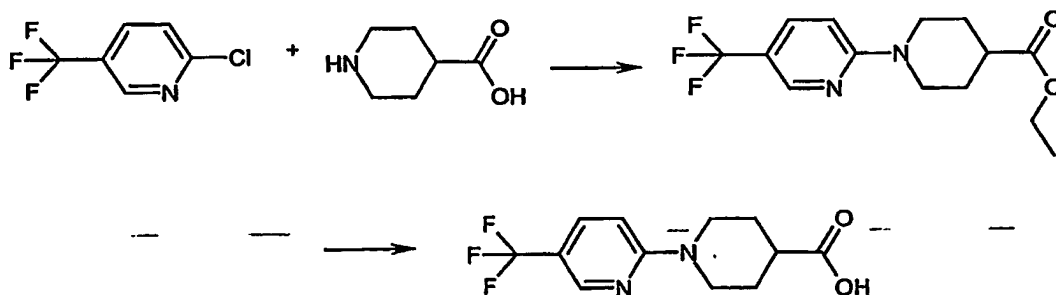
Molecular weight: 239.70

MS (DCI/NH₃): m/z = 240 (M+H)⁺

HPLC (method A): R_t = 3.33 min

[Starting compound 5S]

1-[5-(Trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid



0.500 g (3.18 mmol) of ethyl piperidine-4-carboxylate, 0.866 g (4.77 mmol) of 2-chloro-5-trifluoromethylpyridine and 0.483 g (4.77 mmol) of triethylamine were reacted in dimethyl sulfoxide at 60°C overnight. The reaction mixture was parti-

tioned between ethyl acetate and water, the organic layer was washed with saturated sodium chloride, dried over magnesium sulfate, filtered and evaporated to dryness to yield crude ethyl 1-[5-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylate.

- 5 The crude ethyl 1-[5-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylate was dissolved in 15 ml of methanol and 2.5 ml of water. 535 mg (9.54 mmol) of potassium hydroxide were added and the mixture was reacted at 40°C for 30 min. The mixture was evaporated, the residue was dissolved in water, pH 3 was adjusted with 2N hydrochloric acid and the solid formed was filtered off and dried in vacuo to yield
- 10 471 mg (54 % yield) of 1-[5-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid.

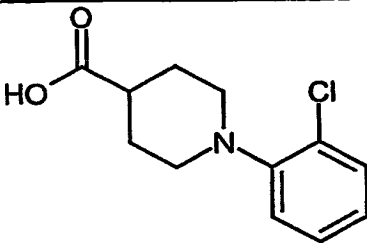
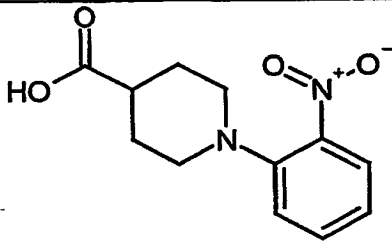
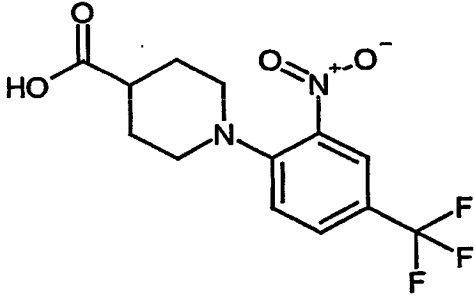
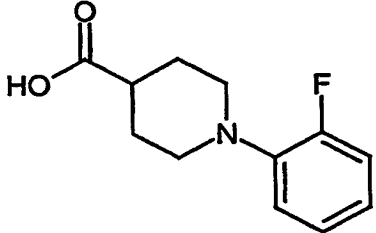
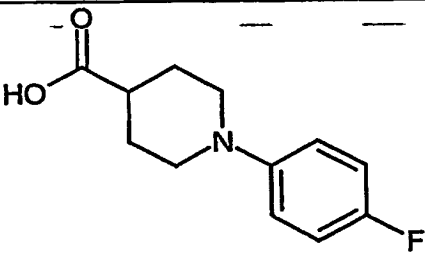
- ¹H NMR (DMSO-*d*₆) δ 1.42-1.60 (m, 2H), 1.81-1.93 (m, 2H), 2.50-2.62 (m, 1H), 3.00-3.14 (m, 2H), 4.21-4.36 (m, 2H), 6.95 (d, 1H), 7.75 (dd, 1H), 8.38 (d, 1H),
- 15 12.25 (s, 1H).

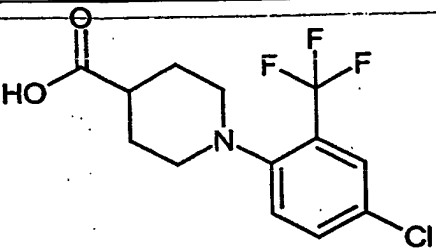
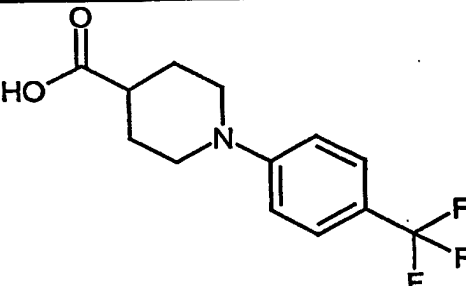
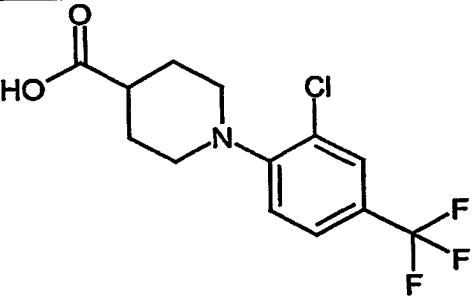
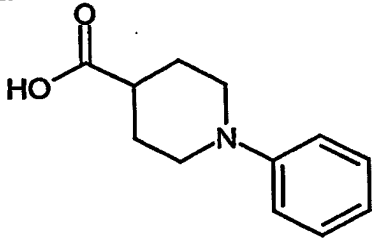
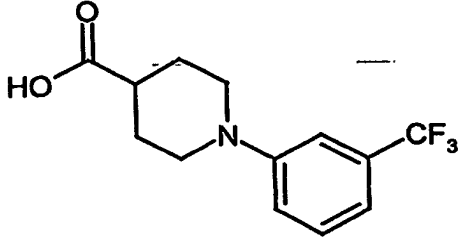
Molecular weight: 274.24

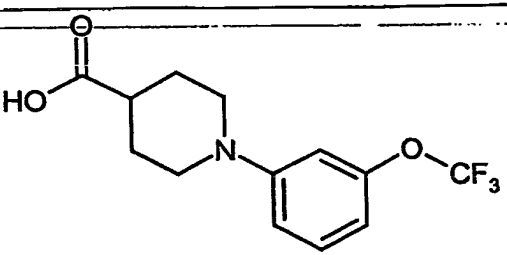
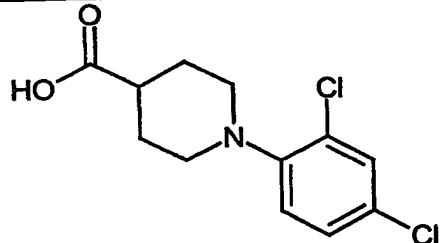
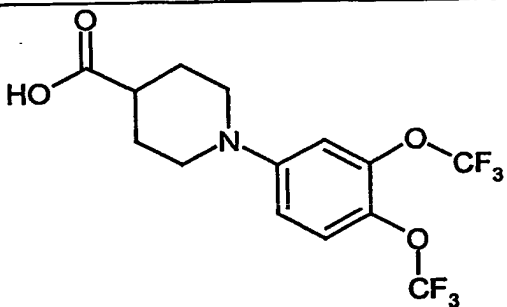
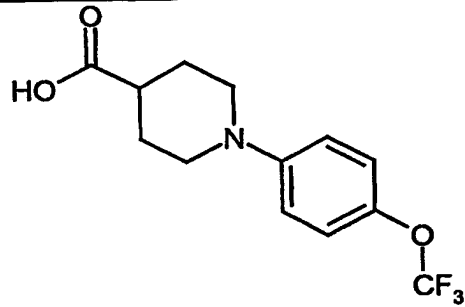
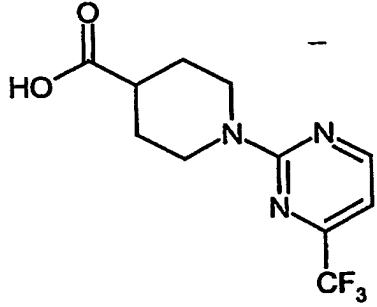
MS: $m/z = 275 (M+H)^+$

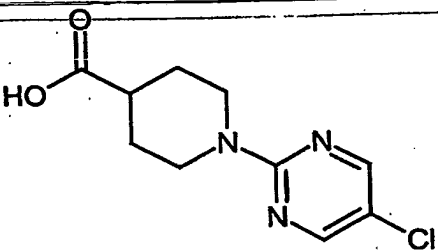
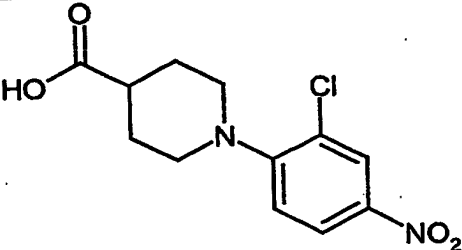
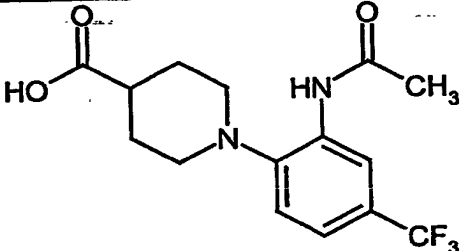
- In a similar manner as described in Starting compound 4S or 5S and by further
- 20 modification of functional groups when needed, Starting compounds 6S to 23S as shown in Table A were synthesized.

Table A

starting compound	structure	M.W.	MS	property
6S		239,70	249	
7S		250,26	251	
8S		318,25	319	
9S		223,25	224	
10S		223,25	224	

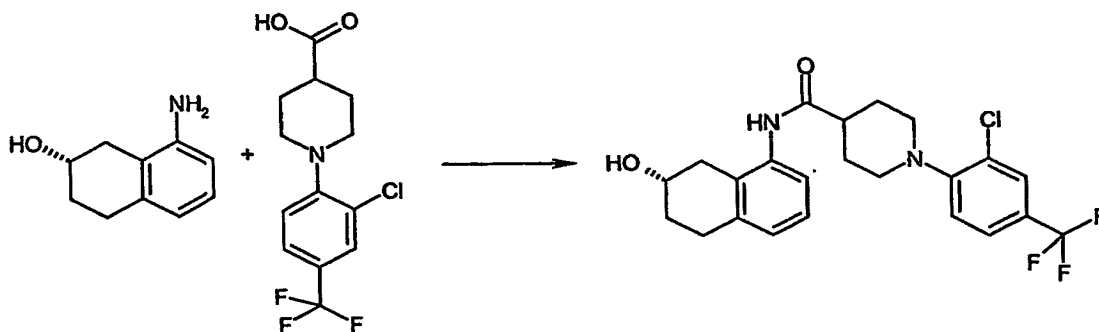
starting compound	structure	M.W.	MS	property
11S		307,70	308	
12S		273,26	274	
13S		307,70	308	HPLC (method A): Rt = 4.79 min
14S		205,26	206	HPLC (method A): Rt = 2.79 min
15S		273,26	274	HPLC (method A): Rt = 3.68 min

starting compound	structure	M.W.	MS	property
16S		289,26	290	HPLC (method A): Rt = 3.82 min
17S		274,15	274	HPLC (method A): Rt = 4.62 min
18S		373,25	374	HPLC (method A): Rt = 4.76 min
19S		289,26	290	HPLC (method A): Rt = 3.71 min
20S		275,23	276	HPLC (method A): Rt = 4.34 min

starting compound	structure	M.W.	MS	property
21S		241,68	242	HPLC (method A): Rt = 3.98 min
22S		284,7	285	HPLC (method A): Rt = 4.39 min
23S		330,3	331	

Example 1-1**1-[2-Chloro-4-(trifluoromethyl)phenyl]-N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl]piperidine-4-carboxamide**

5



10

1-(2-Chloro-4-trifluoromethylphenyl)-piperidine-4-carboxylic acid (0.36 g, 1.16 mmol), (7S)-7-hydroxy-5,6,7,8-tetrahydronaphthaleneamine (0.17 g, 1.05 mmol), 1-hydroxy-1H-benzotriazole (0.17 g, 1.26 mmol) and (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.26 g, 1.37 mmol) were combined in 10 ml of N,N-dimethylformamide under an argon atmosphere and stirred at room temperature overnight. Water was added and the mixture was extracted with ethyl acetate three times. The combined organic phases were dried over magnesium sulfate, evaporated under reduced pressure, and the residue was separated over silica gel in ethyl acetate. Additional purification was achieved by preparative RP-HPLC using a water/ acetonitrile gradient, yielding 1-[2-chloro-4-(trifluoromethyl)phenyl]-N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl]piperidine-4-carboxamide (0.132 g, 28% yield).

15

20

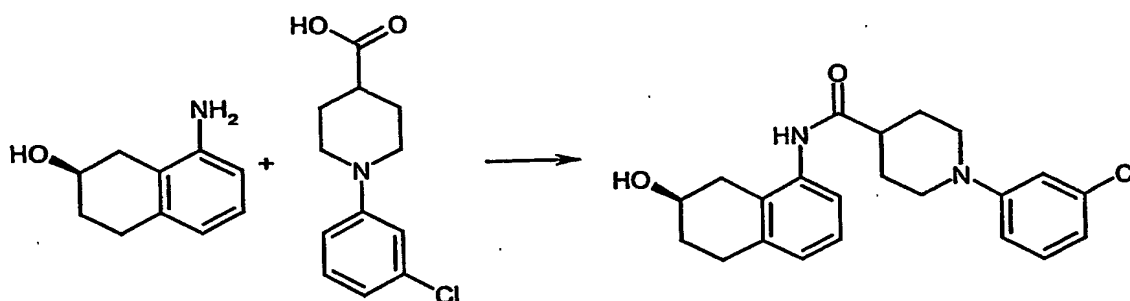
¹H NMR (DMSO-*d*₆) δ 1.53-1.65 (m, 1H), 1.80-2.00 (m, 5H), 2.43 (dd, 1H), 2.55-2.65 (m, 1H), 2.55-2.92 (m, 5H), 3.47 (d, 2H), 3.82-3.94 (m, 1H), 4.80 (d, 1H), 6.92 (d, 1H), 7.06 (t, 1H), 7.15 (d, 1H), 7.34 (d, 1H), 7.65 (d, 1H), 7.77 (s, 1H), 9.19 (s, 1H).

MS (ESIpos): *m/z* = 453 (M+H)⁺

25

HPLC (method B): *R*_t = 4.72 min

Activity Class: A

Example 1-2**1-[3-Chlorophenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-piperidine-4-carboxamide**

120 mg (0.50 mmol) of 1-(3-chlorophenyl)-piperidine-4-carboxylic acid, 74 mg (0.46 mmol) of (7R)-7-hydroxy-5,6,7,8-tetrahydronaphthaleneamine, 74 mg (0.55 mmol) of 1-hydroxy-1H-benzotriazole and 113 mg (0.59 mmol) of (N-(3-dimethylamino-propyl)-N'-ethylcarbodiimide hydrochloride were combined in 3 ml of N,N-dimethylformamide under an argon atmosphere and stirred at room temperature overnight. Ethyl acetate was added, the mixture washed with water and the aqueous phase re-extracted with ethyl acetate three times. The combined organic phases were dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by RP-HPLC in a water/acetonitrile gradient, yielding 57 mg (33% yield) of 1-[3-chlorophenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-carboxamide.

¹H NMR (DMSO-*d*₆) δ 1.51-1.66 (m, 1H), 1.72 (qd, 2H), 1.80-1.94 (m, 3H), 2.42 (dd, 1H), 2.50-2.93 (m, 6H), 3.75-3.94 (m, 3H), 4.77 (d, 1H), 6.75 (dd, 1H), 6.87-6.98 (m, 3H), 7.05 (t, 1H), 7.14 (d, 1H), 7.20 (t, 1H), 9.13 (s, 1H).

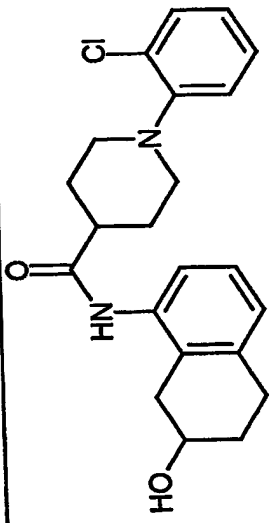
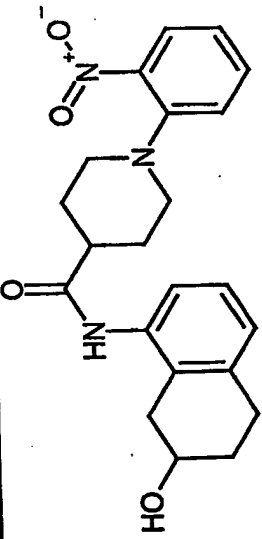
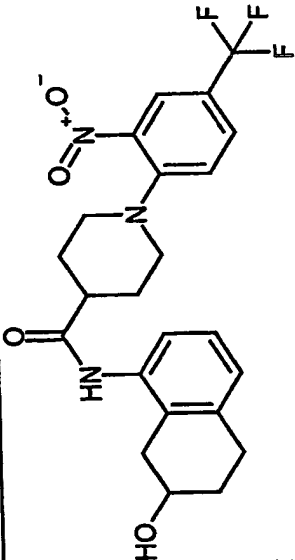
MS (ESIpos): *m/z* = 385 (M+H)⁺

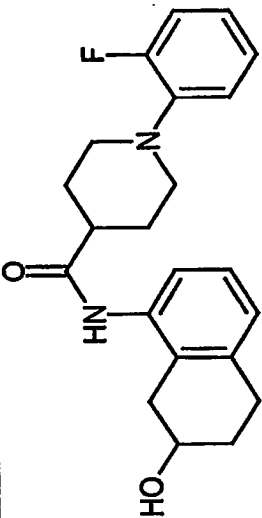
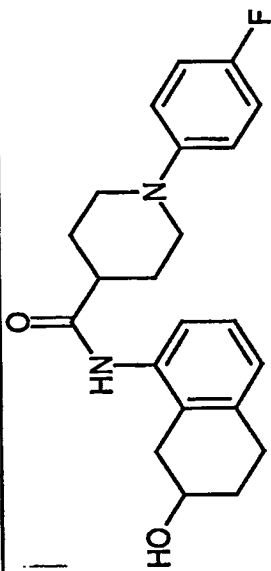
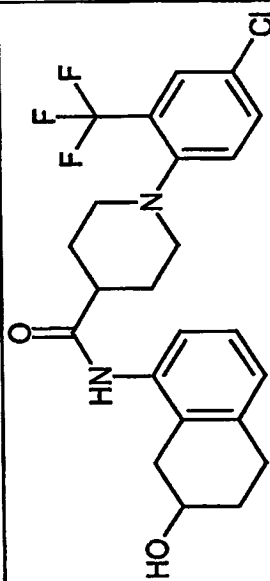
HPLC (method B): *R*_t = 3.80 min

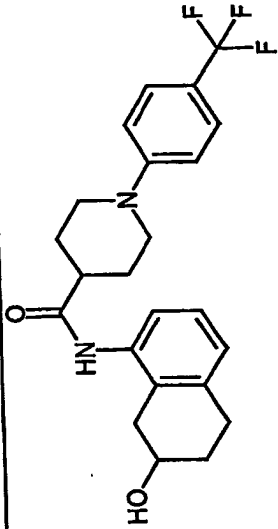
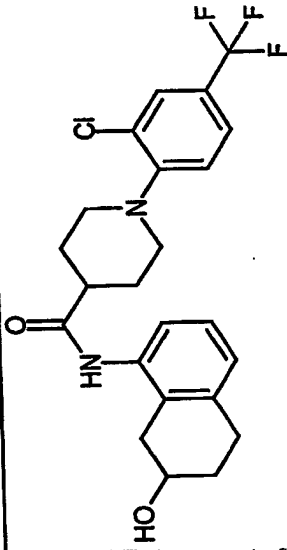
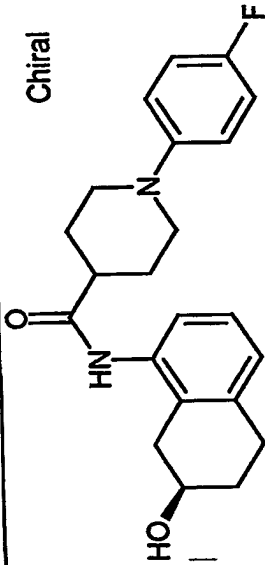
Activity Class: A

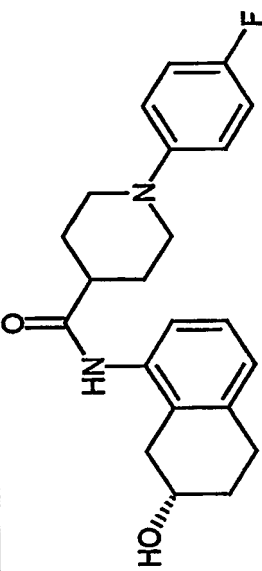
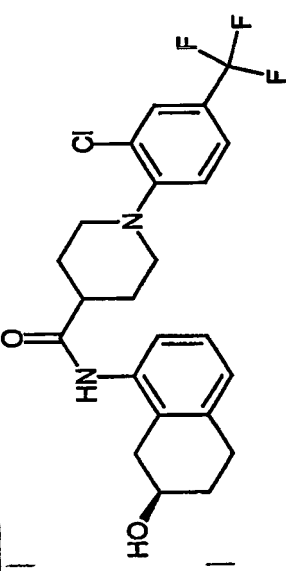
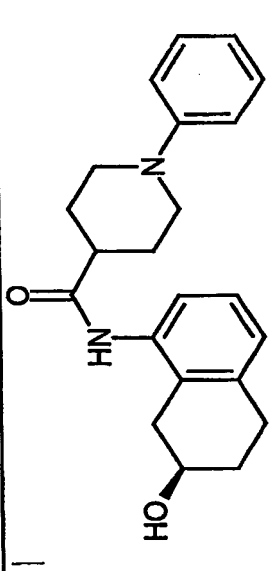
In a similar manner as described in Example 1-1 or 1-2, compounds in Example 1-3 to 1-25 as shown in Table 1 were synthesized.

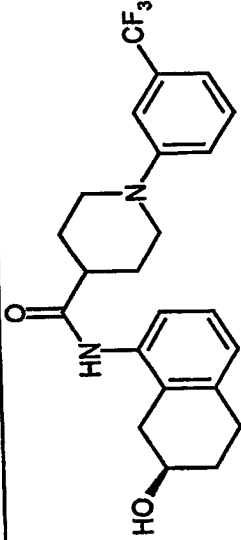
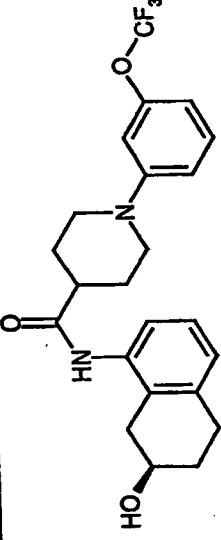
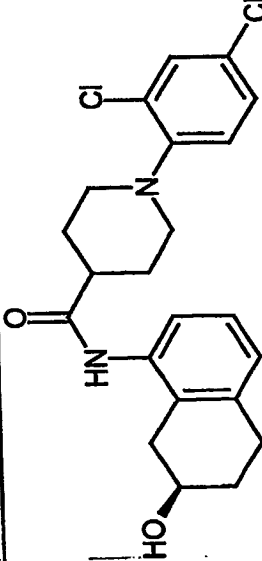
Table 1

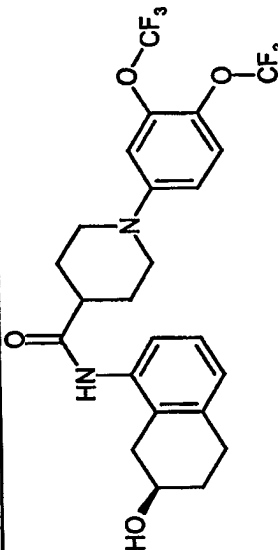
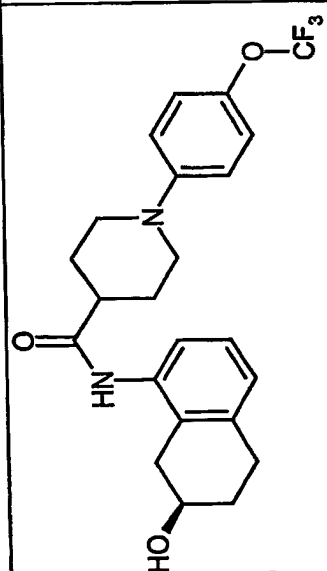
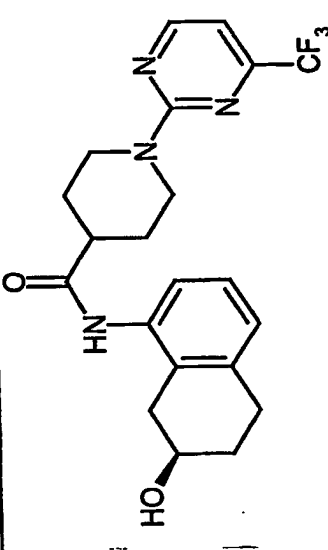
BAY_NO	example #	structure	M.W.	MS	property	NMR	Activity Class
BAY 727220	1-3		384,91	385	mp : 210°C		A
BAY 727224	1-4		395,46	396	mp : 170°C		A
BAY 732328	1-5		463,46	464	mp : 218°C		A

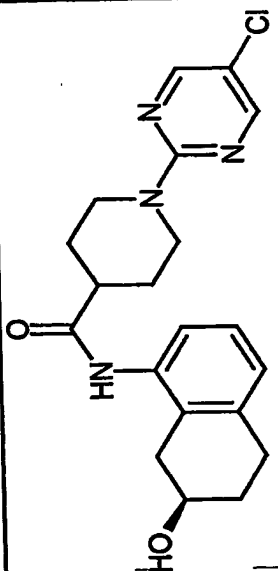
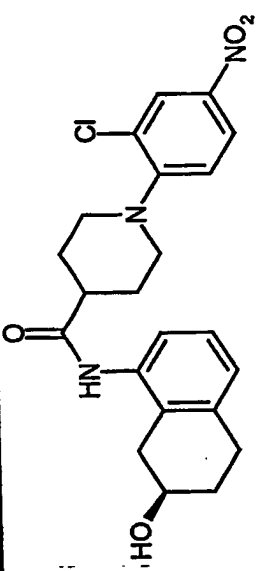
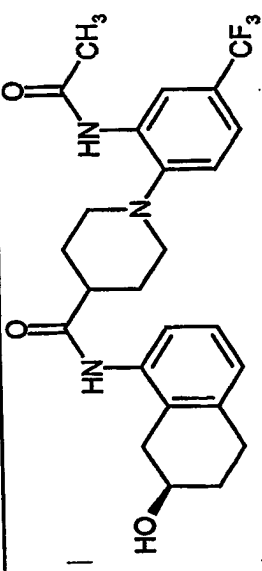
BAY_NO	example #	structure	M.W.	MS	property	NMR	Activity Class
BAY 732330	1-6		368,46	369	mp : 207°C		A
BAY 732331	1-7		368,46	369	mp : 205°C		A
BAY 732332	1-8		452,91	453	mp : 182°C		A

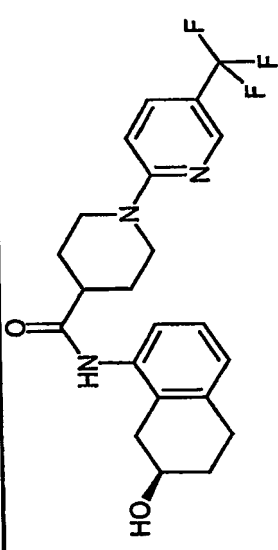
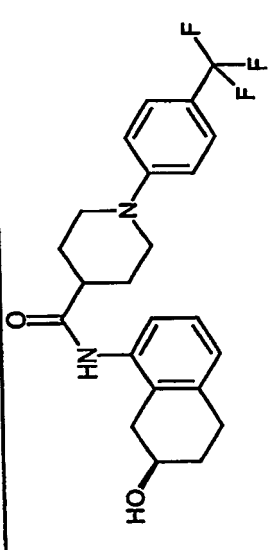
BAY_NO	example #	structure	M.W.	MS	property	NMR	Activity Class
BAY 732333	1-9		418.46	419	mp : 222°C		A
BAY 732334	1-10		452.91	453	mp : 226°C		A
BAY 731401	1-11		368.46	369	mp : 205°C		A

BAY_NO	example #	structure	M.W.	MS	property	NMR	Activity Class
BAY 731402	1-12		368,46	369	mp : 205°C		A
BAY 731403	1-13		452,91	453	mp : 226°C		A
BAY 751538	1-14		350,459	351	HPLC (method A): Rt = 3.57 min	¹ H NMR (DMSO-d6) δ 1.51-1.66 (m, 1H), 1.76 (qd, 2H), 1.82-1.95 (m, 3H), 2.42 (dd, 1H), 2.50-2.65 (m, 1H), 2.65-2.80 (m, 3H), 2.80-2.93 (m, 2H), 3.77 (d, broad, 2H), 3.82-3.94 (m, 1H), 4.77 (d, 1H), 6.76 (t, 1H), 6.88-7.00 (m, 3H), 7.04 (t, 1H), 7.11-7.25 (m, 3H), 9.12 (s, 1H).	A

BAY_NO	example #	structure	M.W.	MS	property	NMR	Activity Class
BAY 751544	1-15		418,457	419	HPLC (method A): Rt = 4.01 min	¹ H NMR (DMSO-d ₆) δ 1.50-1.67 (m, 1H), 1.77-2.03 (m, 5H), 2.43 (dd, 1H), 2.59-2.80 (m, 2H), 2.80-2.96 (m, 4H), 3.61 (d, 2H), 3.83-3.95 (m, 1H), 4.77 (d, 1H), 6.92 (d, 1H), 7.06 (t, 1H), 7.15 (d, 1H), 7.32 (d, 1H), 8.15 (dd, 1H), 8.23 (d, 1H), 9.18 (s, 1H).	A
BAY 751533	1-16		434,456	435	HPLC (method B): Rt = 4.10 min	¹ H NMR (DMSO-d ₆) δ 1.51-1.66 (m, 1H), 1.75 (qd, 2H), 1.81-1.96 (m, 3H), 2.42 (qd, 1H), 2.50-2.65 (m, 1H), 2.65-2.93 (m, 4H), 3.78 (dt, broad, 2H), 3.82-3.94 (m, 1H), 4.77 (d, 1H), 6.91 (d, 1H), 6.98-7.10 (m, 3H), 7.16 (t, 1H), 8.15 (dd, 1H), 9.13 (s, 1H).	A
BAY 751862	1-17		419,35	419	HPLC (method B): Rt = 4.61 min	¹ H NMR (DMSO-d ₆) δ 1.51-1.67 (m, 1H), 1.75-2.02 (m, 5H), 2.42 (dd, 1H), 2.47-2.63 (m, 1H), 2.63-2.79 (m, 3H), 2.79-2.94 (m, 2H), 3.82-3.95 (m, 1H), 4.77 (d, 1H), 6.92 (d, 1H), 7.06 (t, 1H), 7.15 (d, 1H), 7.19 (d, 1H), 7.36 (dd, 1H), 7.53 (d, 1H), 9.14 (s, 1H).	A

BAY_NO	example #	structure	M.W.	MS	property	NMR	Activity Class
BAY 751540	1-18		518,452	519	HPLC (method A): Rt = 4.87 min	¹ H NMR (DMSO-d ₆) δ 1.50-1.81 (m, 3H), 1.81-1.97 (m, 3H), 2.42 (dd, 1H), 2.55-2.95 (m, 6H), 3.79-3.95 (m, 3H), 4.77 (d, 1H), 6.91 (d, 1H), 7.00-7.10 (m, 3H), 7.14 (d, 1H), 7.39 (d, 1H), 9.15 (s, 1H).	A
BAY 748459	1-19		434,456	435	HPLC (method A): Rt = 3.94 min	¹ H NMR (DMSO-d ₆) δ 1.50-1.67 (m, 1H), 1.75 (qd, 2H), 1.80-1.96 (m, 3H), 2.42 (dd, 1H), 2.50-2.93 (m, 6H), 3.78 (d, 2H), 3.82-3.94 (m, 1H), 4.77 (d, 1H), 6.91 (d, 1H), 6.98-7.10 (m, 3H), 7.16 (t, 3H), 9.13 (s, 1H).	A
BAY 744162	1-20		420,433	421	HPLC (method A): Rt = 4.38 min	¹ H NMR (DMSO-d ₆) * 1.68 (d, 1H), 1.73-1.92 (m, 3H), 1.98-2.13 (m, 3H), 2.48-2.66 (m, 2H), 2.78-3.12 (m, 5H), 4.10-4.25 (m, 1H), 4.89 (d, broad, 2H), 6.75 (d, 1H), 6.90-7.00 (m, 2H), 7.15 (t, 1H), 7.58 (d, broad, 1H), 8.49 (d, 1H).	A

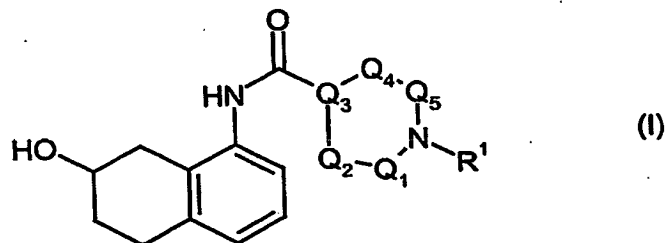
BAY_NO	example #	structure	M.W.	MS	property	NMR	Activity Class
BAY 744339	1-21		386,881	387	HPLC (method A): Rt = 4.11 min	¹ H NMR (DMSO-d ₆) δ 1.50-1.68 (m, 1H), 1.80-1.96 (m, 1H), 2.41 (dd, 1H), 2.64-2.92 (m, 4H), 2.94-3.08 (t, 2H), 3.81-3.95 (m, 1H), 4.63 (d, broad, 2H) 4.76 (d, 1H), 6.91 (d, 1H), 7.04 (t, 1H), 7.13 (d, 1H), 8.41 (s, 2H), 9.14 (s, 1H).	A
BAY 748327	1-22		429,902	430	HPLC (method B): Rt = 4.47 min	¹ H NMR (DMSO-d ₆) δ 1.50-1.67 (m, 1H), 1.77-2.03 (m, 5H), 2.43 (dd, 1H), 2.59-2.80 (m, 2H), 2.80-2.96 (m, 4H), 3.61 (d, 2H), 3.83-3.95 (m, 1H), 4.77 (d, 1H), 6.92 (d, 1H), 7.06 (t, 1H), 7.15 (d, 1H), 7.32 (d, 1H), 8.15 (dd, 1H), 8.23 (d, 1H), 9.18 (s, 1H).	A
BAY 756834	1-23		475,508	476	HPLC (method A): Rt = 4.17 min	¹ H NMR (DMSO-d ₆) δ 1.48-1.72 (m, 1H), 1.80-2.25 (m, 8H), thereof 2.18 (s, 3H), 2.34-2.95 (m, 7H), 3.10-3.27 (m, 2H), 3.80-3.98 (m, 1H), 4.81 (d, 1H), 6.92 (d, 1H), 7.05 (t, 1H), 7.17 (d, 1H), 7.30 (d, 1H), 7.41 (d, 1H), 8.17 (s, 1H), 9.08 (s, 1H), 9.19 (s, 1H).	A

BAY_NO	example #	structure	M.W.	MS	property	NMR	Activity Class
BAY 748450	1-24		419,445	420	HPLC (method A): Rt = 3.68 min	¹ H NMR (DMSO-d6) δ 1.51-1.71 (m, 3H), 1.80-2.00 (m, 3H), 2.41 (dd, 1H), 2.64-2.92 (m, 4H), 2.93-3.12 (m, 2H), 3.81-3.93 (m, 1H), 4.40-4.52 (m, 2H), 4.75 (d, 1H), 6.91 (d, 1H), 6.98 (d, 1H), 7.03 (t, 1H), 7.12 (d, 1H), 7.77 (dd, 1H), 8.41 (d, 1H), 9.15 (s, 1H).	A
BAY 731468	1-25		418,5	419	HPLC (method A): Rt = 4.16 min	¹ H NMR (DMSO-d6) δ 1.52-1.78 (m, 3H), 1.81-1.97 (m, 3H), 2.41 (dd, 1H), 2.60-2.78 (m, 2H), 2.79-2.99 (m, 4H), 3.81-4.01 (m, 3H), 4.81 (d, 1H), 6.91 (d, 1H), 7.01-7.18 (m, 4H), 7.50 (d, 2H), 9.18 (s, 1H).	A

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Claims

1. A hydroxy-tetrahydro-naphthalene derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:



wherein

Q_1, Q_2, Q_4 and Q_5 independently represent $C(R^{11})(R^{12})$,

wherein

R^{11} and R^{12} independently represent hydrogen, phenyl, benzyl, or C_{1-6} alkyl optionally substituted by hydroxy, carboxy, phenyl, benzyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino;

Q_3 represents $C-R^{13}$,

wherein

R^{13} represents hydrogen, phenyl, benzyl, or C_{1-6} alkyl optionally substituted by hydroxy, carboxy, phenyl, benzyl, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, or di(C_{1-6} alkyl)amino;

R^1 represents C_{1-6} alkyl substituted by aryl or heteroaryl,

wherein

5 said aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, hydroxy, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₃₋₈ cycloalkylamino, C₁₋₆ alkoxycarbonyl, phenyl, benzyl, heterocycle, sulfonamide, C₁₋₆ alkanoyl, C₁₋₆ alkanoylamino, carbamoyl, C₁₋₆ alkylcarbamoyl, cyano, C₁₋₆ alkyl optionally substituted by cyano, C₁₋₆ alkoxycarbonyl or
10 mono-, di-, or tri-halogen, C₁₋₆ alkoxy optionally substituted by mono-, di-, or tri- halogen, phenoxy optionally substituted by halogen or C₁₋₆ alkyl, or C₁₋₆ alkylthio optionally substituted by mono-, di-, or tri-halogen, C₃₋₈ cycloalkyl, and heterocycle;

or

15

aryl or heteroaryl,

wherein

20

said aryl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, hydroxy, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₃₋₈ cycloalkylamino, C₁₋₆ alkoxycarbonyl, phenyl, benzyl, heterocycle, sulfonamide, C₁₋₆ alkanoyl, C₁₋₆ alkanoylamino, carbamoyl, C₁₋₆ alkylcarbamoyl, cyano, C₁₋₆ alkyl optionally
25 substituted by cyano, C₁₋₆ alkoxycarbonyl or mono-, di-, or tri-halogen, C₁₋₆ alkoxy optionally substituted by mono-, di-, or tri- halogen, phenoxy optionally substituted by halogen or C₁₋₆ alkyl, or C₁₋₆ alkylthio optionally substituted by mono-, di-, or tri- halogen, C₃₋₈ cycloalkyl, and heterocycle.

30

2. The hydroxy-tetrahydro-naphthalene derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

5

R¹ represents C₁₋₂ alkyl substituted by phenyl, naphthyl, pyridyl, or pyrimidyl,

wherein

10

15

said phenyl, naphthyl, pyridyl and pyrimidyl are optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₃₋₈ cycloalkylamino, C₁₋₆ alkoxy carbonyl, phenyl, benzyl, C₁₋₆ alkanoyl, C₁₋₆ alkanoylamino, carbamoyl, C₁₋₆ alkylcarbamoyl, cyano, C₁₋₆ alkyl optionally substituted by mono-, di-, or tri-halogen, C₁₋₆ alkoxy optionally substituted by mono-, di-, or tri- halogen, phenoxy optionally substituted by halogen or C₁₋₆ alkyl, or C₁₋₆ alkylthio optionally substituted by mono-, di-, or tri- halogen;

20

or

phenyl, naphthyl, pyridyl, or pyrimidyl

25

wherein

30

said phenyl, naphthyl, pyridyl and pyrimidyl are optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₃₋₈ cycloalkylamino, C₁₋₆ alkoxy carbonyl, phenyl, benzyl, C₁₋₆ alkanoyl, C₁₋₆ alkanoylamino, carbamoyl,

C₁₋₆ alkylcarbamoyl, cyano, C₁₋₆ alkyl optionally substituted by mono-, di-, or tri-halogen, C₁₋₆ alkoxy optionally substituted by mono-, di-, or tri- halogen, phenoxy optionally substituted by halogen or C₁₋₆ alkyl, or C₁₋₆ alkylthio optionally substituted by mono-, di-, or tri- halogen.

5

3. The hydroxy-tetrahydro-naphthalene derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

10

wherein

R¹ represents phenyl, pyridyl, or pyrimidyl,

wherein

15

said phenyl, pyridyl and pyrimidyl are optionally substituted with one or more substituents selected from the group consisting of halogen, nitro, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₃₋₈ cycloalkylamino, C₁₋₆ alkoxycarbonyl, phenyl, benzyl, C₁₋₆ alkanoyl, C₁₋₆ alkanoylamino, carbamoyl, C₁₋₆ alkylcarbamoyl, cyano, C₁₋₆ alkyl optionally substituted by mono-, di-, or tri-halogen, C₁₋₆ alkoxy optionally substituted by mono-, di-, or tri- halogen, phenoxy optionally substituted by halogen or C₁₋₆ alkyl, or C₁₋₆ alkylthio optionally substituted by mono-, di-, or tri- halogen.

20

25

4. The hydroxy-tetrahydro-naphthalene derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,

wherein

30

Q₁, Q₂, Q₄ and Q₅ represent CH₂;

Q_3 represents CH_3 ;

R^1 represents phenyl, pyridyl, or pyrimidyl

5

wherein

10

said phenyl, pyridyl and pyrimidyl are optionally substituted with one or more substituents selected from the group consisting of chloro, bromo, fluoro, nitro, methoxy, trifluoromethyl, trifluoromethoxy and C_{1-6} alkanoylamino.

15

5. The hydroxy-tetrahydro-naphthalene derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein said hydroxy-tetrahydro-naphthalene derivative of the formula (I) is selected from the group consisting of:

20

1-(2-Chlorophenyl)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)piperidine-4-carboxamide;

N-(7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-1-(2-nitrophenyl)piperidine-4-carboxamide;

N-(7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-1-[2-nitro-4-(trifluoromethyl)phenyl]piperidine-4-carboxamide;

25

1-(2-Fluorophenyl)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)piperidine-4-carboxamide;

1-(4-Fluorophenyl)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)piperidine-4-carboxamide;

30

1-[4-Chloro-2-(trifluoromethyl)phenyl]-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)piperidine-4-carboxamide;

N-(7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-1-[4-(trifluoromethyl)phenyl]piperidine-4-carboxamide;

- 1-[2-Chloro-4-(trifluoromethyl)phenyl]-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)piperidine-4-carboxamide;
- 5 1-(4-Fluorophenyl)-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-carboxamide;
- 1-(4-Fluorophenyl)-N-[(7S)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-carboxamide;
- 10 1-[2-Chloro-4-(trifluoromethyl)phenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-carboxamide;
- 1-[2-Chloro-4-(trifluoromethyl)phenyl]-N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl]piperidine-4-carboxamide;
- 1-[3-Chlorophenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-carboxamide;
- N-[(7R)-7-Hydroxy-1-phenyl-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-carboxamide;
- 15 N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[3-trifluoromethyl-phenyl]piperidine-4-carboxamide;
- N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[3-trifluoromethoxy-phenyl]piperidine-4-carboxamide;
- 20 1-[2,4-Dichlorophenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-carboxamide;
- 1-[3,4-Bis[trifluoromethoxy]phenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydro-naphthalen-1-yl]piperidine-4-carboxamide;
- N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[4-trifluoromethoxy-phenyl]piperidine-4-carboxamide;
- 25 N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[4-trifluoromethyl-pyrimidin-2-yl]-piperidine-4-carboxamide;
- 1-[5-Chloropyrimidin-2-yl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-carboxamide;
- 1-[2-Chloro-4-nitrophenyl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-carboxamide;
- 30

1-[3-(Acetylamino)-5-(trifluoromethyl)pyridin-2-yl]-N-[(7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]piperidine-4-carboxamide;

N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[5-(trifluoromethyl)-pyridin-2-yl]piperidine-4-carboxamide; and

5 N-[(7R)-7-Hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]-1-[4-trifluoromethyl-phenyl]piperidine-4-carboxamide.

6. A medicament comprising the hydroxy-tetrahydro-naphthalene derivative of the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.
- 10 7. The medicament as claimed in claim 6, further comprising one or more pharmaceutically acceptable excipients.
- 15 8. The medicament as claimed in claim 6, wherein said hydroxy-tetrahydro-naphthalene derivative of the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is a VR1 antagonist.
9. The medicament as claimed in claim 6 for the treatment and/or prevention of an urological disorder or disease.
- 20 10. The medicament as claimed in claim 9, wherein said urological disorder or disease is urge urinary incontinence or overactive bladder.
- 25 11. The medicament as claimed in claim 6 for the treatment and/or prevention of pain.
12. The medicament as claimed in claim 11, wherein said pain is chronic pain, neuropathic pain, postoperative pain, or rheumatoid arthritic pain.

13. The medicament as claimed in claim 6 for the treatment and/or prevention of
a disorder or disease related to pain.

5 14. The medicament as claimed in claim 13, wherein said disorder or disease
related to pain is neuralgia, neuropathies, algesia, nerve injury, ischaemia,
neurodegeneration, or stroke.

10 15. The medicament as claimed in claim 6 for the treatment and/or prevention of
an inflammatory disorder or disease.

16. The medicament as claimed in claim 15, wherein said inflammatory disorder
or disease is asthma or COPD.

15 17. Use of compounds according to claim 1 for manufacturing a medicament for
the treatment and/or prevention of an urological disorder or disease.

18. Use of compounds according to claim 1 for manufacturing a medicament for
the treatment and/or prevention of pain.

20 19. Use of compounds according to claim 1 for manufacturing a medicament for
the treatment and/or prevention of an inflammatory disorder or disease.

25 20. Process for controlling an urological disorder or disease in humans and
animals by administration of a VR1-antagonistically effective amount of at
least one compound according to claim 1.

30 21. Process for controlling pain in humans and animals by administration of a
VR1-antagonistically effective amount of at least one compound according to
claim 1.

22. Process for controlling an inflammatory disorder or disease in humans and animals by administration of a VR1-antagonistically effective amount of at least one compound according to claim 1.

01. Okt. 2003

TETRAHYDRO-NAPHTHALENE DERIVATIVES

ABSTRACT

This invention relates to tetrahydro-naphthalene derivatives and salts thereof which are useful as active ingredients of pharmaceutical preparations.

The tetrahydro-naphthalene derivatives of the present invention have an excellent activity as VR1 antagonists and are useful for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of urinary incontinence, urge urinary incontinence, overactive bladder, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke, inflammatory disorders, asthma and COPD.

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